

## **REMARKS**

Claims 1, 3-5, 7-11, 14, 16-24, 27, 28, 37, 38, 40-51, 61-64, 67, 68, 76-79, and 83-85 are pending in the application. Claims 77-79, 83 and 84 are presently withdrawn from consideration.

### *Claim Rejections under 35 U.S.C. §§102 and 103*

The withdrawal of the rejections under 35 U.S.C. §102 is gratefully acknowledged.

The rejection of claims 1, 3-5, 7-11, 14, 16-24, 37, 38, 40-51, 61-64, 67, 68 and 76 as being unpatentable under 35 103(a) over BE 612725 (Fredrick Leonard) or Ishida Junko et al. or WO 97/37658 (Spinelli et al.) has been maintained however, and added claim 85 has been rejected on the same basis. These rejections are again respectfully traversed based on the following arguments and the amendments to the claims herein.

Claim 1 has previously been amended to exclude compounds wherein the R<sub>3</sub> group is methoxy. As indicated in Table 34 (page 89) of the application, harmine derivatives of this type, wherein R<sub>3</sub> is methoxy, have been found to have considerable neurotoxicity, whereas similar compounds wherein R<sub>3</sub> is not methoxy, as presently claimed, have distinctly reduced neurotoxicity.

The cited compounds (24 and 25) of Ishida Junko et al. are R<sub>3</sub> methoxy-substituted compounds, and the reference lacks any teaching of the increased neurotoxicity associated with the R<sub>3</sub> methoxy-substituted compounds. One of ordinary skill in the art would not be led by this cited art to select the pharmacologically acceptable (non-neurotoxic) non-R<sub>3</sub> methoxy-substituted compounds, as presently claimed, from among the many compounds disclosed.

Similarly, WO 97/37658 (Spinelli et al.) teaches compounds wherein R<sub>3</sub> is C<sub>1</sub>-C<sub>4</sub> alkoxy, therefore including R<sub>3</sub> methoxy-substituted compounds, again with no teaching of the increased neurotoxicity associated with the R<sub>3</sub> methoxy-substituted compounds. Moreover, the reference teaches not  $\beta$ -carboline compounds, which have saturated third ring, but specifically tetrahydroharmine  $\beta$ -carboline compounds, which have an unsaturated third ring. The lack of saturation in the third ring of the compounds taught by the reference represents a substantial chemical difference, and is submitted to teach away from the claimed  $\beta$ -carboline compounds. Again, one of ordinary skill in the art would not be led by this cited art to select the pharmacologically acceptable (non-neurotoxic) non-R<sub>3</sub> methoxy-substituted  $\beta$ -carboline compounds, as presently claimed, from among the many tetrahydroharmine compounds disclosed.

Finally, BE 612725 (Fredrick Leonard) discloses a very large genus of compounds. The present invention relates to a much narrower set of compounds selected to combine anti-tumor

activity with low neurotoxicity. The prior art disclosure does not read on the pending claims with sufficient specificity to anticipate the claims. (*See, e.g.,* MPEP 2131.03 citing *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006)). It is important to note that BE 612725 does not provide a finite number of identified, predictable known options for arriving at the claimed invention. Instead, the disclosure provides a lengthy list of possible compounds, some of which might or might not combine the sought-after anti-tumor activity with low neurotoxicity of the claimed compounds of the present invention. The disclosure is simply too broad to provide sufficient direction to one of ordinary skill in the art to reach the claimed invention. In such circumstances, the Supreme Court and the Court of Appeals for the Federal Circuit have indicated that a finding of obviousness is inappropriate (*See, KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385, 1395-97 (2007); and *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009)).

Accordingly, withdrawal of the rejections under 35 U.S.C. 103(a) is respectfully requested.

#### *Dependent Claims*

The remaining rejected claims depend directly or indirectly from claim 1 and are therefore submitted to be patentable for at least the same reason.

It is further submitted that a number of dependent claims have independent bases for patentability beyond those discussed above. As one example, amended claim 19 is directed to the compounds in which R<sub>3</sub> is an ethoxy group. It is respectfully submitted that this species is nowhere taught or suggested by the cited art and is patentable for this reason in addition to the reasons presented above with respect to the more general claims.

#### *Claim Rejections under 35 U.S.C. §112*

The claims have been rejected under the first and second paragraphs of section 112 as indefinite or lacking written description. Regarding claim 24, the claim has been amended in accordance with the Examiner's suggestion to address the section 112, second paragraph, issue. Regarding the recitation of "pharmaceutically acceptable salts" in claim 1, it is respectfully submitted that support is found for this terminology in the specification, particularly, for example, in the Objects of the Invention section at page 2, first paragraph which states that the invention relates to harmine derivatives with anti-tumor activity and lower neurotoxicity. It is previously disclosed that the compounds of the present application are intended for use as pharmaceuticals, particularly anti-tumor medicaments (see prior paragraph and Field of Invention section on page 1). In the second paragraph on page 3, it is clear that the subject 9-substituted  $\beta$ -carboline compounds presently claimed and their salts are included within the scope of the invention. Altogether, it is

respectfully submitted that this disclosure provide support for the recitation of “pharmaceutically acceptable salts” in claim 1. Further, the recitation of a substituent on the formula of claim 1 being a salt is submitted not to be inconsistent with the deletion of the “X” term from the formula. Thus, it is submitted that there is appropriate antecedent basis for the terminology of the dependent claims. Withdrawal of the rejections under 35 U.S.C. §112 is therefore respectfully requested.

*Other Issues*

It is understood that upon allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim.

It is further understood that rejoinder of non-elected claims is possible if these claims require or are amended to require all the limitations of an allowable claim. Accordingly, in accordance with MPEP 821.04(a), if any elected claim is found to be allowable Applicants respectfully request the opportunity for rejoinder of non-elected claims.

*Conclusion*

Applicants believe that all pending claims are allowable and respectfully request a Notice of Allowance for this application from the Examiner. Should the Examiner believe that a telephone conference would expedite the prosecution of this application the undersigned can be reached at the telephone number set out below. If any additional fees are due in connection with the filing of this amendment, the Commissioner is authorized to charge such fees to Deposit Account 504480 (Order No. CPALP003).

Respectfully submitted,  
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